Table A-24
Mesothelioma Deaths among Asbestos Insulation Workers
Selikoff and Seidman (1991)

Years After First Exposure Range	Mean	Person Years	Observed Pleural	Peritoneal	Total	Predicted
(<15)	12.5	61655	0	0	0	0.2
(15-19)	17.5	52710	2	3	5	4.6
(20-24)	22.5	57595	10	8	18	23.4
(25-29)	27.5	50519	33	40	73	56.3
(30-34)	32.5	37166	40	65	105	88.0
(35-39)	37.5	20340	33	58	91	87.9
(40-44)	42.5	10201	17	42	59	71.9
(45-49)	47.5	5257	27	31	58	55.5
(50+)	55	6151	11	38	49	106.3
Totals		301593	173	285	458	494.1

Duration = 25 Years and Exposure Concentration = 15 f/ml

$K_M * 10^8$	1.3
(90% Confidence Interval)	(1.2, 1.4)
Goodness of Fit P-value	< 0.001

Table A-25
Lung Cancer Mortality among Workers in a Pennsylvania Textile Factory
McDonald et al. (1983b)

mppcf-y Range	mppcf-y Mean	f-y/ml	SMR	Observed	Expected	Predicted α = 1	Predicted α = 0.519
(< 10)	5	15	66.9	21	31.4	34.1	20.7
(10 - 20)	15	45	83.6	5	6.0	7.5	5.6
(20 - 40)	30	90	156	10	6.4	9.7	8.8
(40 - 80)	60	180	160	6	3.8	7.6	8.3
(>= 80)	110	330	416.1	11	2.6	7.6	9.6
Totals				53	50.2	66.4	53.0

	α = 1 (fixed)	α = 0.519 (MLE)
K_L * 100	0.57	1.8
(90% Confidence Interval)	(0.27, 0.94)	(0.75, 4.5)
Goodness of Fit P-value	0.08	0.76
Test of H_0: α = 1 P-value	0.01	

Table A-26
Mesothelioma Mortality among Pennsylvania Textile Plant Workers
McDonald et al. (1983b)

Years After First Exposure	Duration	f/ml	Person Years	Observed	Predicted
15.5	9.18	6.96	17179	6	0.2
24	9.18	6.96	40868	10	8.2
41	9.18	6.96	9840	7	14.6
Totals			67887	23	23.0
$K_M * 10^8$			1.1		
(90% Confidence Interval)			(0.76, 1.5)		
Goodness of Fit P-value			< 0.001		

Table A-27
Lung Cancer Mortality among Rochdale Asbestos Textile Factory
Peto et al. (1985)

particle-yr/ml Range	Mean	f-y/ml	Observed	Expected	Predicted α = 1	Predicted α = 1.10
(< 1000)	209	5.92	34	29.5	30.4	33.2
(1000 - 2000)	1409	39.92	8	7.7	9.2	9.8
(2000 - 3000)	2511	71.13	11	6.6	9.0	9.4
(3000 - 4000)	3474	98.41	6	5.7	8.5	8.8
(4000 - 5000)	4551	128.92	10	4.3	7.2	7.2
(>= 5000)	9057	256.57	24	10.8	25.2	24.6
Totals			93	64.6	89.6	93.0

		α = 1 (fixed)	α = 1.10 (MLE)
K_L * 100		0.52	0.41
(90% Confidence Interval)		(0.28, 0.79)	(0.12, 0.87)
Goodness of Fit	P-value	0.72	0.63
Test of H_0: α = 1	P-value	0.57	

Table A-28
Mesothelioma Mortality among Rochdale Asbestos Textile Factory
Peto et al. (1985)

Years After First Exposure				Person		
Range	Mean	Duration	f/ml	Years	Observed	Predicted
(0-19)	11.5	0.5	9.12	28015	0	0.01
(20-24)	22.5	0.5	9.12	4668	0	0.2
(25-29)	27.5	0.5	9.12	3470	0	0.3
(30-34)	32.5	0.5	9.12	2041	0	0.3
(35-39)	37.5	0.5	9.12	840	0	0.2
(>=40)	42	0.5	9.12	402	0	0.1
(0-19)	11.5	3	9.12	4786	0	0.003
(20-24)	22.5	3	9.12	877	0	0.2
(25-29)	27.5	3	9.12	632	0	0.3
(30-34)	32.5	3	9.12	421	0	0.3
(35-39)	37.5	3	9.12	238	0	0.3
(>=40)	42	3	9.12	148	1	0.2
(0-19)	11.5	7.5	9.12	8521	0	0.01
(20-24)	22.5	7.5	9.12	1417	0	0.5
(25-29)	27.5	7.5	9.12	1104	0	0.9
(30-34)	32.5	7.5	9.12	707	0	1.1
(35-39)	37.5	7.5	9.12	383	0	0.9
(>=40)	42	7.5	9.12	249	0	0.9
(0-19)	11.5	15	9.12	4814	0	0.003
(20-24)	22.5	15	9.12	1423	0	0.5
(25-29)	27.5	15	9.12	870	0	0.9
(30-34)	32.5	15	9.12	470	3	1.0
(35-39)	37.5	15	9.12	204	0	0.7
(>=40)	42	15	9.12	102	1	0.5
(20-24)	22.5	25	9.12	848	1	0.3
(25-29)	27.5	25	9.12	935	1	1.0
(30-34)	32.5	25	9.12	600	2	1.3
(35-39)	37.5	25	9.12	257	1	1.0
(>=40)	42	25	9.12	122	0	0.8
(30-34)	32.5	35	9.12	86	0	0.2
(35-39)	37.5	35	9.12	107	0	0.4
(>=40)	42	35	9.12	103	0	0.7
Totals				69861	10	16.1

$K_M * 10^8$	1.3
(90% Confidence Interval)	(0.74, 2.1)
Goodness of Fit P-value	0.80

APPENDIX B:
REPORT ON THE PEER CONSULTATION WORKSHOP TO DISCUSS A PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK

Report on the Peer Consultation Workshop to Discuss a Proposed Protocol to Assess Asbestos-Related Risk

Prepared for:

U.S. Environmental Protection Agency
Office of Solid Waste and Emergency Response
Washington, DC 20460

EPA Contract No. 68-C-98-148
Work Assignment 2003-05

Prepared by:

Eastern Research Group, Inc.
110 Hartwell Avenue
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FINAL REPORT
May 30, 2003

NOTE

This report was prepared by Eastern Research Group, Inc. (ERG), an EPA contractor, as a general record of discussion for the peer consultation workshop on a proposed protocol to assess asbestos-related risk. This report captures the main points of scheduled presentations, highlights discussions among the panelists, and documents the public comments provided at the meeting. This report does not contain a verbatim transcript of all issues discussed, and it does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. EPA will use the information presented during the peer consultation workshop to determine whether the proposed risk assessment methodology can be used to support decisions at asbestos-contaminated sites. Except as specifically noted, no statements in this report represent analyses by or positions of EPA or ERG.

CONTENTS

CONTENTS (Continued)

Appendices

LIST OF ABBREVIATIONS

ATSDR	Agency for Toxic Substances and Disease Registry
EPA	U.S. Environmental Protection Agency
ERG	Eastern Research Group, Inc.
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
NIOSH	National Institute for Occupational Safety and Health
PCM	phase contrast microscopy
SEM	scanning electron microscopy
SVF	synthetic vitreous fibers
TEM	transmission electron microscopy
µm	micrometers

EXECUTIVE SUMMARY

Eleven expert panelists participated in a peer consultation workshop to review a proposed protocol to assess asbestos-related risks. The protocol is documented in the report, "Technical Support Document for a Protocol to Assess Asbestos-Related Risk, Parts I and II" (Berman and Crump 1999, 2001). At the end of the 2½-day workshop, which was open to the public, the expert panelists drafted the following summary of their findings:

The peer consultation panel strongly endorsed the conceptual approach of developing an updated cancer risk assessment methodology that takes into account fiber type and fiber dimension. The opportunity is at hand to use substantial new information from epidemiology, experimental toxicology, and exposure characterization on what continues to be an extremely important societal issue—assessing the health risks associated with environmental and occupational exposures to asbestos. The panel recommended that EPA proceed in an expeditious manner to consider the panelists' conclusions and recommendations with a goal of having an updated asbestos risk assessment methodology. It is important that EPA devote sufficient resources so that this important task can be accomplished in a timely and scientifically sound manner. The panel urges that additional analyses underpinning the document, preparation of documentation, and further review be carried out in an open and transparent manner.

Prior to the workshop, the participants received draft copies of the "Methodology for Conducting Risk Assessments at Asbestos Superfund Sites Part 1: Protocol" and "Part 2: Technical Background Document." The panelists generally found that these documents did not provide a complete and transparent description of how the data were analyzed to support the conclusions presented. The incomplete documentation of methodology precluded the replication of the findings, in advance of the meeting, by several panelists. The methodology used was clarified by the comprehensive presentations that Drs. Berman and Crump made at the workshop. However, future drafts of these documents must

clearly describe the methodologies and include sufficient data, perhaps in appendices, such that the findings can be replicated.

The panelists made the following conclusions and recommendations:

- **Measurement methods.** Continuing advances have been made in the application of exposure measurement technology for asbestos fibers during the past two decades. These advances include the use of transmission electron microscopy (TEM) and allied techniques (e.g., energy dispersive x-ray detection, or EDS) as an alternative to phase contrast microscopy (PCM), thereby allowing the bivariate (i.e., length and width) characterization of fibers and fiber type. The proposed risk assessment methodology incorporates these advances in the development of an exposure index. The panel was in agreement that this aspect of the new risk assessment methodology represents a substantial advance over the existing methodology.

- **Integration of exposure and risk assessment models.** A key aspect of the proposed risk assessment methodology is a linking of specific exposure characterization methodology with exposure-response coefficients. It has been emphasized that any change in the exposure characterization metrics must be accompanied by changes in the exposure-response coefficients of the risk assessment models. This was emphasized in the report and the panelists endorsed this view.

- **Access to additional raw data sets.** The panelists strongly recommended that EPA make every attempt to acquire and analyze raw data sets from key human epidemiological studies. Where possible, it would also be desirable to obtain bivariate (i.e., length and diameter) fiber exposure information for these re-analyses. Several panelists believed that review of additional data sets offers substantial opportunity for improving the proposed risk assessment methodology. In the event that raw data cannot be obtained due to confidentiality reasons or other restrictions, the panelists suggested that the authors consider asking those who have access to the data to conduct the necessary statistical analyses and communicate their results directly to EPA for further consideration.

- **Fiber diameter.** The proposed risk assessment methodology uses a diameter cut-off of 0.5 micrometers (μm) for considering fibers. The report states that fibers 0.7 μm in diameter can reach the respiratory zone of the lung. A few panel members indicated that the fiber diameter cut-off could be as high as 1.5 μm during oral breathing. The 0.4 μm cut-off came from rat data, but larger diameters would be expected to be respirable in humans. There was general agreement that the diameter cut-off should be between 0.5 and 1.5 μm. This issue is deserving of further analysis.

- **Fiber length.** The Berman and Crump analyses made a significant contribution by obtaining and analyzing membrane filters from the animal inhalation studies in Edinburgh and conducting quality-assured bivariate length and distribution analyses by TEM—thereby greatly reducing the uncertainty of the exposure side of the exposure-response relationship for chronic fiber exposure in rats. Unfortunately, correspondingly detailed information on bivariate size distribution is not available for humans. This leads to the need to use the animal data, although one must always recognize the uncertainties associated with interspecies extrapolations such as anatomic characteristics and respirability between species. Future analyses may benefit from using other available laboratory animal data sets and human data sets.

  The fiber length distributions for the human cohort exposures are much more uncertain. For the Wittenoom, Quebec, and South Carolina cohorts, there are limited fiber length distribution data based on TEM analysis from historic membrane filter samples, but only fiber categories longer than 5 μm and longer than 10 μm were counted. For all other cohorts, the measurements were limited to PCM fiber counts for all fibers greater than 5 μm in length in some, and particle counts (10x objective) on midget impinger samples in others. Both methods do not measure thin fibers, do not discriminate between asbestos and other mineral particles, and provide no information on the concentrations of fibers longer than 10, 20, or 40 μm, or inter-laboratory variations in optical resolution and counting rules. As one approach to addressing the varying uncertainty in assessing exposure in the different studies, Berman and Crump used the available information to make adjustments to the uncertainty ranges in the exposure-response coefficients. The workshop panel welcomed this initiative but suggested alternative approaches (see "Methods," below).

  Some panelists felt that an Exposure Assessment Workshop, with participants having a broad range of expertise, could evaluate the uncertainties in historic occupational data sets' exposure measurements. They felt such a workshop could result in a more confident assessment of exposure-response relationships for populations exposed to a variety of amphiboles, chrysotile, and mixtures. With incorporation of other available knowledge on fiber type, process, smoking (if available), and the relative number of excess lung cancer and mesothelioma, it may well be possible to gain a much clearer understanding of the roles of these variables as causal factors for these asbestos-associated cancers. In addition, the workshop would prove valuable in further discussion of mineralogical, geological, and industrial hygiene issues with regard to application of the model to risk assessment in environmental sites of concern.

  The Berman and Crump index assigns zero risk to fibers less than 5 μm in length. Fibers between 5 and 10 μm are assigned a risk that is one three-hundredth of the risk assigned to fibers longer than 10 μm. Panelists agreed that there is a considerably greater risk for lung cancer for fibers longer than 10 μm. However, the panel was uncertain as to an exact cut size for length and the magnitude of the relative potency. The panelists also agreed that the available

data suggest that the risk for fibers less than 5 μm in length is very low and could be zero. This specific issue was addressed by an expert panel convened by the Agency for Toxic Substances and Disease Registry (ATSDR) in October 2002. Some panelists suggested that, for mesothelioma, greater weight should perhaps be assigned to fibers in the 5 to 10 μm length range and to thinner fibers.

- **Fiber type.** For *mesothelioma*, the panelists supported the use of different relative carcinogenic potencies for different fiber types. The panelists unanimously agreed that the available epidemiology studies provide compelling evidence that the carcinogenic potency of amphibole fibers is two orders of magnitude greater than that for chrysotile fibers. There was some discussion about the precise ratio expressed due to questions about the availability of exposure data in existing studies (e.g., Wittenoom). There was recognition that time since first exposure is an important factor in determining risk for mesothelioma and some discussion is needed on the importance of duration and intensity of exposure.

  For *lung cancer*, the panelists had differing opinions on the inferences that can be made on the relative potency of chrysotile and amphibole fibers. Some panelists supported the finding that amphibole fibers are 5 times or more potent for lung cancer than are chrysotile fibers. Other panelists did not think the statistical analyses in the draft methodology document supports this relative potency and wondered if additional review of the epidemiological data might identify factors other than fiber type (e.g., industry considered) that provide further insights on the matter. These other factors can then be considered when the risk assessment is applied.

- **Cleavage fragments.** The panel knew of little data to directly address the question as to whether cleavage fragments of equal durability and dimension as fibers would have similar or dissimilar potency for lung cancer. The general view is that data indicate that durability and dimension are critical to pulmonary pathogenesis. Therefore, it is prudent at this time to assume equivalent potency for cancer in the absence of other information to the contrary. Consideration of conducting a rat inhalation study using tremolite cleavage fragments was recommended to address this issue. For mesothelioma, it was viewed that thin fibers greater than 5 μm in length are more important. Cleavage fragments that do not meet these criteria would not contribute to risk of mesothelioma.

- **Other amphiboles.** The panel agreed with the report's conclusion that the potency of currently regulated and unregulated amphibole fibers should be considered equal based on the reasoning that similar durability and dimension would be expected to result in similar pathogenicity.

- **Methods.** The panelists extensively discussed the approach to conducting the meta-analysis of the large number of epidemiological studies. A number of the panelists urged that consideration be given to using more traditional approaches that would include development and application of specific criteria for inclusion of studies into the exposure-response analysis, examination of

heterogeneity and sources of the heterogeneity, and the use of sensitivity analysis to identify influential studies.

The panelists also urged, in the study-specific analysis, exploration of alternative exposure-response models other than the lung cancer and mesothelioma risk models EPA has been using since 1986. This would possibly include non-linear response models (e.g., log-linear models), examination of separate effects for concentration and duration, time since first exposure, time since cessation of exposure, possibly dropping the "α factor," and different methods for measurement error. The adequacy of different models should be examined using goodness of fit statistics across all studies. The possibility of internal analyses should be re-examined (i.e., it may be possible to obtain partial data, such as age-specific person years data, from authors). Exploration of non-linearity should also include shape of the curve in the low exposure area.

The panelists also urged alternative approaches to meta-analyses. In particular, panelists recommended meta-regression using original (untransformed) exposure-response coefficients, in which predictor variables include the estimated percentage of amphiboles, percentage of fiber greater than 10 μm, and categorical grouping of studies according to quality. Original exposure-response coefficient variances should be used in conjunction with random effects models in which residual inter-study variation is estimated. Analyses restricted to long latency and a predictor variable for industry type should be considered. A priori distribution for inter-study residual variance might also be considered. Meta-regression will allow simple inspection of likelihoods to consider the importance of different predictor variables. Sensitivity analyses should be conducted in which the inclusion or exclusion of specific studies or groups of studies is evaluated.

- **Cigarette smoking.** Most panelists felt strongly that future analyses need to pay more attention to the effects of smoking on the lung cancer exposure-response model and extrapolations to risk. However, the current data sets have variable and limited information available on smoking. The panelists noted that smoking is the primary cause for lung cancer, but the lung cancer dose-response relationship for smoking is complex due to the effects of smoking duration, intensity, and cessation.

  The impact of smoking has effects on both the estimation and the application of the model for projecting risk of lung cancer due to asbestos exposure. This may be an especially critical issue for low-exposure extrapolation. With respect to estimation, accepting the form of the proposed model, the effect of smoking may require different K_L values for smokers and non-smokers. The panelists recognized that there is limited epidemiologic data to address this issue, but recommend that it be investigated. With respect to applying the model to make risk projections for any future cohort, the background rate of lung cancer employed in the model needs to be carefully determined to capture the smoking behavior of the cohort.

- **Localized tremolite exposures.** During the course of public comments, the panel received input from several individuals who expressed concerns about environmental exposures to tremolite asbestos from localized geologic formations in California. The individuals suggested that inadequate attention had been given to characterization of the exposures to residents of these communities. While the panel was not in a position or charged with the evaluation of this issue, the panel did feel that this was a potentially serious matter deserving of attention by the appropriate public health authorities. Evaluation of these kinds of situations would benefit from the use of the improved risk assessment methodology being considered.

The remainder of this report summarizes the discussions and observations that led to these findings, reviews the panelists' comments on many topics not listed in this executive summary, and documents the observer comments provided at the workshop.

1. INTRODUCTION

This report summarizes a peer consultation by 11 expert panelists of a proposed protocol to assess asbestos-related risks. Contractors to the U.S. Environmental Protection Agency (EPA) developed the proposed protocol, which is documented in a report titled: "Technical Support Document for a Protocol to Assess Asbestos-Related Risk" (Berman and Crump 2001). The purpose of the peer consultation workshop was to provide EPA feedback on the scientific merit of the proposed protocol. The peer consultation workshop took place in a meeting open to the public on February 25–27, 2003, in San Francisco, California.

This report summarizes the technical discussions among the expert panelists and documents comments provided by observers. These discussions largely focused on three topic areas: interpretations of the epidemiology and toxicology literature, the proposed exposure index, and general questions about key assumptions and inferences in the protocol. The remainder of this introductory section presents background information on the protocol (Section 1.1), describes the scope of the peer consultation workshop (Section 1.2), and reviews the organization of this report (Section 1.3).

1.1 Background

EPA's current assessment of asbestos toxicity is based primarily on an asbestos review completed in 1986 (EPA 1986) and has not changed substantially since that time. The 1986 assessment considers six mineral forms of asbestos and all asbestos fiber sizes longer than 5 micrometers (μm) to be of equal carcinogenic potency. However, since 1986, asbestos measurement techniques and the understanding of how asbestos exposure contributes to disease have improved substantially. To incorporate the knowledge gained over the last 17 years into the agency's toxicity assessment for asbestos, EPA contracted with Aeolus, Inc., to develop a proposed methodology for conducting asbestos risk assessments. The proposed methodology distinguishes between fiber sizes and fiber types in estimating

potential health risks related to asbestos exposure. The methodology also proposes a new exposure index for estimating carcinogenic risk.

As a key step in determining the scientific merit of the proposed risk assessment methodology, EPA decided to obtain expert input on the draft report through a peer consultation workshop. The purpose of the workshop was to obtain feedback from subject-matter experts during the development stage of the proposed risk assessment methodology; the workshop was not an official peer review. Eastern Research Group, Inc. (ERG), organized and implemented the peer consultation workshop under a contract to EPA.

1.2 Scope of the Peer Consultation Workshop

The peer consultation involved many activities before the workshop (see Section 1.2.1), at the workshop (see Section 1.2.2), and after the workshop (see Section 1.2.3). The following subsections describe these activities.

1.2.1 Activities Prior to the Peer Consultation Workshop

This section describes the major activities ERG and the expert panelists conducted prior to the peer consultation workshop:

- ***Select expert panelists.*** ERG selected the expert panelists for the peer consultation workshop. ERG sought to compile a panel of experts with broad experience and expertise in the following disciplines: toxicology, epidemiology, biostatistics, asbestos sampling and analytical methods, EPA's human health risk assessment guidelines, and asbestos-related environmental and occupational health issues. Appendix A lists the expert panelists ERG selected, and Appendix B includes brief biographies that summarize the panelists' areas of expertise.

  Every panelist is either a senior scientist, physician, or researcher with extensive experience in the aforementioned fields, as demonstrated by peer-reviewed publications, awards, and service

to relevant professional societies. To ensure the peer consultation offered a balanced perspective, ERG intentionally selected expert panelists with a broad range of affiliations (e.g., academia, consulting, state and federal agencies). When searching for panelists, ERG asked all candidates to disclose real or perceived conflicts of interest.

- ***Prepare a charge to the expert panelists.*** ERG worked with EPA to prepare written guidelines (commonly called a "charge") for the peer consultation workshop. The charge includes 12 specific questions, organized into 4 topic areas. Discussions at the workshop largely addressed the technical issues raised in the charge, but the expert panelists were encouraged to discuss other relevant matters that were not specifically addressed in the charge questions. A copy of the charge is included in Appendix B.

- ***Distribute review documents and other relevant information.*** Several weeks prior to the peer consultation workshop, ERG sent every panelist copies of the charge and the proposed risk assessment methodology (Berman and Crump 2001). These items formed the basis of the technical discussions at the workshop. In addition, ERG distributed several additional publications on related topics (see Table 1, at the end of this section, for list of the publications). The supplemental publications were provided largely in response to panelists' requests for further background information on selected issues. The panelists also circulated publications amongst themselves on specific topics. Finally, one of the meeting chairs noted for the record that, upon arriving in San Francisco, he also received a memo and copies of many abstracts and other information from Cate Jenkins of EPA. The meeting chair offered to share these materials with other panelists during the workshop.

- ***Obtain and compile the panelists' premeeting comments.*** After receiving the workshop materials, the panelists were asked to prepare their initial responses to the charge questions. Booklets containing the premeeting comments were distributed to the expert panelists before the workshop and were made available to observers at the workshop. These initial comments are included in this report, without modification, as Appendix B. It should be noted that the premeeting comments are preliminary in nature. Some panelists' technical findings may have changed after the premeeting comments were submitted.

1.2.2 Activities at the Peer Consultation Workshop

The 11 expert panelists and approximately 75 observers attended the peer consultation workshop, which was held at the Westin St. Francis Hotel in San Francisco, California, on February 25–27, 2003. The workshop was open to the public, and the workshop dates and times were announced in the

Federal Register. Appendix C lists the observers who confirmed their attendance at the workshop registration desk. The workshop schedule generally followed the agenda, presented here as Appendix D.

The workshop began with introductory remarks from Ms. Jan Connery (ERG), the facilitator of the peer consultation. Ms. Connery welcomed the expert panelists and observers, stated the purpose of the workshop, identified the document being reviewed, and explained the procedure for observers to make comments. Mr. Richard Troast (EPA) then provided background information on the review document and EPA's ongoing efforts to assess asbestos toxicity (see Section 1.1). Mr. Troast identified the main differences between EPA's existing asbestos risk assessment methodology (EPA 1986) and the proposed methodology (Berman and Crump 2001). Mr. Troast noted that the expert panelists' feedback will ultimately help EPA complete its update of asbestos health risks for the Integrated Risk Information System (IRIS); he clarified that the final IRIS update will be subject to peer review or Science Advisory Board review before being implemented. Following these opening remarks, Dr. Wayne Berman and Dr. Kenny Crump—the authors of the proposed methodology—presented detailed information on the review document; Section 2 of this report summarizes their presentations.

After the background presentation, Dr. Roger McClellan and Dr. Leslie Stayner chaired the technical discussions that followed. For the remainder of the meeting, the panelists engaged in free-flowing discussions when answering the charge questions and addressing additional topics not specified in the charge. Observers were given the opportunity to provide verbal comments three different times during the workshop; these observer comments are documented in Appendix E. Representatives from EPA and the document authors provided clarifications on the proposed methodology periodically throughout the 2½-day workshop.

1.2.3 Activities Following the Peer Consultation Workshop

The primary activity following the peer consultation workshop was preparing this summary report. A technical writer from ERG who attended the meeting prepared a draft of this report, which ERG distributed to the 11 expert panelists and asked them to verify that the draft accurately reflects the tone and substance of the panelists' discussions at the workshop. After incorporating the panelists' suggested revisions to the draft report, ERG submitted the final report (i.e., this report) to EPA.

1.3 Report Organization

The structure of this report follows the order of the technical discussions during the meeting. Section 2 summarizes Dr. Berman and Crump's background presentations. Sections 3 through 6 are records of the panelists' discussions on the four main topic areas: interpretations of the epidemiology and toxicology literature (Section 3), the proposed exposure index (Section 4), general questions (Section 5), and conclusions and recommendations (Section 6). Finally, Section 7 provides references for all documents cited in the text.

The appendices to this report include background information on the peer consultation workshop. This information includes items that were on display at the workshop and items generated since the workshop (e.g., a final list of attendees). The appendices contain the following information:

- List of the expert panelists (Appendix A).
- The panelists' premeeting comments, the charge to the reviewers, and brief bios of the expert panelists (Appendix B).
- List of registered observers of the peer consultation workshop (Appendix C).
- Agenda for the peer consultation workshop (Appendix D).
- Observer comments provided at the peer consultation workshop (Appendix E).
- Observer post-meeting comments (Appendix F).

Table 1
References ERG Provided to the Expert Panelists

Berman, DW and Crump K. 1999. Methodology for Conducting Risk Assessments at Asbestos Superfund Sites; Part 1: Protocol. Final Draft. Prepared for U.S. Environmental Protection Agency. February 15, 1999.
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EPA 1986. Airborne Asbestos Health Assessment Update. U.S. Environmental Protection Agency. EPA 600/8-84-003F. 1986.
NIOSH Interdivisional Fiber Subcommittee Report. Prepared by the NIOSH Interdivisional Fiber Subcommittee. 1999.

2. BACKGROUND ON THE PROPOSED PROTOCOL TO ASSESS ASBESTOS-RELATED RISK

This section summarizes presentations given by the principal authors of the proposed risk assessment methodology. These presentations were given because several panelists asked ERG, prior to the peer consultation workshop, if the authors would provide detailed background information on how the methodology was developed. This section reviews the major presentation topics, but does not present the panelists' comments on the proposed protocol. Sections 3 through 6 document the expert panelists' technical feedback on the protocol.

- ***Motivation for developing the proposed protocol.*** Dr. Berman identified several reasons for developing the updated protocol for assessing asbestos-related risks. These reasons include EPA's existing asbestos models being inconsistent with inferences from the scientific literature, the need for having uniformly-applied sampling and analytical procedures to measure asbestos characteristics most predictive of risk, and the belief that EPA's current asbestos risk assessment methodology may not be adequately protective in some circumstances. To improve upon the current methodology, the authors intended to develop a risk assessment model that adequately predicts cancer risk in all studied environments and can therefore be applied with much greater confidence to environments that have not been studied. Dr. Berman outlined the general approach taken to develop the proposed protocol, as summarized in the following bulleted items.

  Dr. Berman provided background information on and definitions for asbestos, other fibrous structures, asbestos morphology, and cleavage fragments. He also described the capabilities and limitations of the analytical techniques that have been used to characterize asbestos exposures, such as midget impingers, phase contrast microscopy (PCM), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Dr. Berman explained how differences in these analytical techniques must be critically evaluated when comparing results reported in all epidemiological and other types of studies that examine asbestos exposure. Dr. Berman also stressed that it is not just differences in analytical techniques, but choice of specific methods for each analytical technique that affects results. Further information on these topics is included in Chapter 4 of the proposed protocol (Berman and Crump 2001).

- ***Re-analysis of human epidemiological data.*** Dr. Crump described how the authors evaluated the human epidemiological data. He displayed a list of the studies that were considered, noting that he had access to raw, individual-level data for three occupational cohorts: chrysotile textile workers in South Carolina, United States; crocidolite miners in

Wittenoom, Australia; and chrysotile miners and millers in Quebec, Canada. All data sets with exposure data were considered in the analysis, and criteria were not established for selecting studies. Dr. Crump then presented findings for asbestos-related risks for lung cancer and mesothelioma.

For lung cancer, Dr. Crump first reviewed EPA's existing lung cancer model for asbestos exposure (see equation 6.1 in the proposed protocol), which relates the relative risk of lung cancer mortality linearly to cumulative asbestos exposure, with a 10-year lag time. Dr. Crump noted that the model predicts that relative risk for developing lung cancer remains constant after asbestos exposure ceases—an assumption he showed was reasonably consistent with findings from epidemiological studies. Dr. Crump also discussed how the model assesses interactions between exposures to cigarette smoke and to asbestos—an issue the panelists revisited several times later in the workshop (e.g., see Section 3.1.1 and the executive summary). Dr. Crump presented a series of tables and figures demonstrating the adequacy of multiple lung cancer models: first using EPA's existing lung cancer model, next using a modified version of the model that accounts for differences in the background rates of lung cancer, and finally using the proposed lung cancer model, which considers an exposure index that assigns greater carcinogenic potency to amphibole fibers and to longer fibers.

Similarly, Dr. Crump reviewed the performance of EPA's mesothelioma model for asbestos exposures (see equation 6.11 in the proposed protocol), which predicts that mesothelioma risks vary linearly with the average asbestos exposure and increase quadratically with time from onset of exposure. Dr. Crump presented several tables and graphs indicating how well EPA's existing model and the proposed protocol fit the human epidemiological data. He made several conclusions about the existing risk model, including that mesothelioma risk coefficients varied considerably across the cohorts and the risk coefficients were generally higher for cohorts exposed primarily to amphibole fibers, compared to those exposed primarily to chrysotile fibers. Dr. Crump also noted that the data did not support consideration of a sub-linear or threshold dose-response relationship. This latter point generated considerable discussion later in the workshop (e.g., see Section 4.3).

Dr. Crump then described the meta-analysis the authors conducted to evaluate the relative potency of amphibole and chrysotile fibers. First, he explained how the authors weighted the different studies in the meta-analysis, based on uncertainty factors assigned to the individual studies. Dr. Crump identified the four uncertainty factors and described generally how each factor was assigned. Sources of uncertainty included representativeness of air sampling data, the availability of conversion factors to express exposures in terms of PCM concentrations, and whether data on exposure duration were available. Dr. Crump then highlighted the main conclusions from the meta-analysis. For lung cancer, the meta-analysis suggested that amphibole fibers are approximately five times more potent than are chrysotile fibers, but the difference in potency was not statistically significant (i.e., the authors could not reject the hypothesis that

chrysotile fibers and amphibole fibers are equally potent). For mesothelioma, the meta-analysis suggested that chrysotile fibers are 0.002 times as potent as amphibole fibers, and the difference in potency was statistically significant.

- ***Inferences drawn from the broader literature.*** Dr. Berman described how the authors incorporated inferences from the broader scientific literature into the proposed protocol. He reviewed key findings on how various mechanisms are biologically related to how asbestos causes disease. These mechanisms included respiration, deposition, degradation, clearance, translocation, and tissue-specific biological responses. Chapter 7 of the review document provides detailed information on the relevance of these mechanisms, with emphasis on the influence of fiber type and fiber dimension.

- ***Derivation of the exposure index.*** Dr. Berman explained how the authors derived the exposure index, which is largely based on an earlier re-analysis (Berman et al. 1995) of six animal inhalation studies conducted by a single laboratory. That re-analysis found that lung tumor incidence is adequately predicted using an exposure index that assigns no carcinogenic potency to fibers shorter than 5 μm, relatively low carcinogenic potency to fibers with lengths between 5 and 40 μm and diameters less than 0.4 μm, and the greatest carcinogenic potency to fibers longer than 40 μm and thinner than 0.4 μm. However, these findings could not be applied directly to the human epidemiological data, because the epidemiological studies do not include exposure measurements that quantify the relative amounts of asbestos fibers shorter and longer than 40 μm.

  Dr. Berman noted that the proposed protocol includes an *ad hoc* assumption that the fiber size weighting factors optimized from the laboratory animal studies can be applied to humans, but with a length cut-off of 10 μm in the exposure index, rather than a cut-off of 40 μm. Dr. Berman emphasized that this assumption was made to model the critical characteristics of asbestos in a manner that reasonably captures cancer risks observed across multiple epidemiological studies. He acknowledged that asbestos potency is likely a continuous function of fiber length, but the exposure measurements from the available animal and epidemiological studies do not support incorporating such a continuous function in the exposure-response model. The panelists commented on the proposed exposure index when discussing topic area 3 (see Section 4).

  Dr. Berman also noted that the authors selected a conservative set of dose-response coefficients (see Table 6-30 of the review document), rather than using the optimized ones from the animal studies (see Table 6-29). However, the conservative and optimized dose-response coefficients were reasonably consistent: none of the conservative coefficients differed by more than a factor of 4 from the corresponding optimized ones.

- ***Conclusions regarding proposed protocol.*** Dr. Berman indicated that the proposed protocol is substantially more consistent with inferences documented in the scientific literature (i.e., that

long, thin structures contribute most to risk) than EPA's existing risk assessment methodology. Further, the proposed protocol provides a better fit to cancer risks observed in the human epidemiological studies than does EPA's existing model, and the proposed protocol appears to underestimate risks of lung cancer and mesothelioma less frequently and to a lesser degree than the existing approach. Finally, by recommending use of a standardized analytical method that links directly to the exposure index, the proposed protocol will help ensure that future risk assessments are conducted in a consistent fashion and their results can be readily compared from one study to the next.

3. COMMENTS ON TOPIC AREA 1: INTERPRETATIONS OF THE EPIDEMIOLOGY AND TOXICOLOGY LITERATURE

This section summarizes the panelists' discussions on the interpretations of the epidemiology and toxicology literature. The meeting co-chairs—Dr. McClellan and Dr. Stayner—facilitated the discussions on this topic area, which focused first on lung cancer (see Section 3.1) and then on mesothelioma (see Section 3.2). This section presents a record of discussion of the topics mentioned during the workshop. Several panelists referred to their premeeting comments (see Appendix B) for additional suggestions for how the review of epidemiology and toxicology literature can be improved.

3.1 Lung Cancer

The panelists discussed at length whether the epidemiology and toxicology literature support the proposed protocol's finding for how lung cancer potency varies with fiber type and fiber length. This section summarizes these discussions, first on fiber type (Sections 3.1.1 and 3.1.2) and then on fiber length (Sections 3.1.3 and 3.1.4). General issues regarding the lung cancer evaluation are presented in Section 3.1.5.

3.1.1 Lung Cancer and Fiber Type: Inferences from the Epidemiology Literature

According to the proposed risk assessment methodology, amphibole fibers have a 5-fold greater lung cancer potency than do chrysotile fibers. The panelists had differing opinions on whether this finding is consistent with the epidemiology literature. On the one hand, some panelists indicated that the epidemiology literature is consistent with amphibole fibers being more potent for lung cancer, though the magnitude of this increase may not be known precisely. One panelist noted, for example, that multiple analyses (e.g., Hodgson and Darnton 2000, Berman and Crump 2001, and the statistical analyses a panelist presented during this discussion) all point to a consistent increased lung cancer potency for amphibole fibers compared to chrysotile fibers, albeit a small increase. On the other hand, other

panelists did not believe the epidemiology literature supports this conclusion, for reasons stated below. Finally, other panelists were not convinced that the epidemiology literature supports the higher lung cancer potency for amphibole fibers, but they believed the difference in potency seems likely based on evidence from the animal toxicology studies (see Section 3.1.3) and lung burden studies. A summary of the panelists' discussion on this topic follows:

- ***Comments on specific publications.*** Several panelists cited specific studies to support their positions on the relative lung cancer potency of chrysotile and amphibole fibers, but the panelists often had differing opinions on the inferences that should be drawn. The panelists mentioned the following specific studies:

  - Some panelists noted that a recent re-analysis of 17 cohorts (Hodgson and Darnton 2000) indicates that the lung cancer potency for amphibole fibers is 10 to 50 times greater than that for chrysotile fibers. One panelist did not agree with this finding, due to the crude approach the article uses to characterize relative potency. Specifically, this panelist noted that carcinogenic potency was calculated by dividing the overall relative risk for a given cohort by the average exposure for the entire cohort, even for cohorts where the data support more sophisticated exposure-response modeling. He was particularly concerned about the authors' decision to omit the cohort of South Carolina textile workers from the meta-analysis. This decision was apparently based on the South Carolina cohort being an outlier, due to its much higher lung cancer potency when compared to other studies. The panelist noted, however, that the lung cancer risk for the South Carolina cohort is not unusually high when compared to other cohorts of textile workers. The panelist was concerned that omitting this study might have biased the article's finding regarding relative lung cancer potency. No other panelists discussed the review article.

  - One panelist cited a study of Quebec chrysotile miners and millers (Liddell et al. 1997, 1998) that reports that increased lung cancer risk was limited to the mining region with the highest level of tremolite asbestos, after correction for smoking and exposure. The article was distributed to the panelists on the first day of the workshop, but no panelists commented further on the study.

  - One panelist noted that his review of multiple textile cohorts (Stayner, Dankovic, and Lemen 1996) found relatively small differences in lung cancer potency, even though some of the cohorts were exposed to asbestos mixtures containing different proportions of amphibole fibers.

- One panelist indicated that further evidence on how fiber types relates to lung cancer potency can be gleaned from epidemiological studies that were not included in the meta-analysis due to inadequate exposure data for exposure-response modeling. Examples include a study of non-occupationally exposed women from two chrysotile asbestos mining regions (Camus et al. 1998) and a study of railroad workers employed by shops that processed different proportions of amphibole fibers (Ohlson et al. 1984). Both studies, she noted, provide evidence that amphibole fibers exhibit greater lung cancer potency. This panelist added that studies of auto mechanics have provided no convincing evidence of increased lung cancer due to chrysotile exposure, though she acknowledged that the absence of an effect might reflect the short fiber length in the friction brake products. One panelist cautioned about inferring too much from these studies regarding fiber type because they were not controlled for other factors, such as fiber length and level of exposure.

- One panelist added that a recent study of a cohort of Chinese asbestos plant workers (Yano et al. 2001) should be considered in future updates to the proposed protocol; the workers in the cohort had increased risks for lung cancer and were reportedly exposed to "amphibole-free" chrysotile asbestos. However, another panelist cited a publication (Tossavainen et al. 2001) that indicates that asbestos from many Chinese chrysotile mines actually does contain varying amounts of amphibole fibers.

- Several panelists noted that the proposed protocol's meta-analysis found a 5-fold difference in lung cancer potency between amphibole and chrysotile fibers. However, other panelists indicated that the reported difference was not statistically significant. Some panelists had additional reservations about the authors' meta-analysis, as summarized in the following bulleted items.

- ***Comments on the meta-analysis approach.*** Several panelists commented on alternate approaches the authors could have used to conduct their meta-analysis of the epidemiology studies. One panelist noted that the lung cancer potencies reported by the various studies exhibit considerable heterogeneity. In such cases, meta-regression is conventionally used to identify which factors account for the variability in the results (i.e., in the lung cancer potencies). This panelist suggested that the meta-analysis should have considered other factors in addition to fiber type and dimension; such other factors could include industry, follow-up time for the cohort, and estimated percentage of amphibole fibers in the exposures, to the extent that data on these other factors are available.

  To demonstrate how more detailed investigation might reveal further insights, one panelist presented his own initial statistical analysis of the epidemiological studies. This analysis used a fixed effects model and a random effects model, both inverse weighted by the variance of the studies. His analysis examined how industry and fiber type contribute to the heterogeneity

observed among the cohorts and found that the industry of the cohort appears to be a stronger predictor than fiber type. The panelist explained that the purpose of displaying his statistical analysis was to highlight how other approaches to conducting meta-analysis can offer different insights on the epidemiological data. This panelist recommended that the authors conduct similar meta-regression analyses to investigate the importance of various variables on the lung cancer potency.

This panelist also demonstrated how a sensitivity analysis might yield additional information on influential studies. Using a fixed effects model, the panelist first showed how lung cancer potency factors (K_L) vary with exposure to chrysotile fibers, amphibole fibers, and mixed fiber types. When all epidemiological studies were considered in his analysis, the amphibole fibers were found to be three times more potent than the chrysotile fibers. When the cohort of chrysotile miners and millers from Québec was omitted from this analysis, however, the amphibole fibers were found to be nearly two times *less* potent than the chrysotile fibers. Conversely, when the cohort of textile workers from South Carolina was omitted, the amphibole fibers were found to be more than ten times more potent than the chrysotile fibers. Given that the conclusions drawn about the relative potency of chrysotile and amphibole fibers appear to be highly sensitive to whether single studies are omitted from the analysis, this panelist was more skeptical about whether the increased potency of amphibole fibers is a robust finding. He recommended that the authors, when completing the proposed protocol, conduct similar sensitivity analyses to help reveal the factors or studies that appear to contribute most to lung cancer.

Another panelist agreed with this feedback, and provided further comments on the meta-analysis, noting that these analyses typically start with establishing criteria for study inclusion. After selecting studies to evaluate, she said, various statistical analyses can be used to test hypotheses and to understand the concordance and disparity among the individual studies. The panelist thought such an approach is needed to help understand the variability in potency factors observed across the multiple studies and to identify for further analysis the studies found to be most descriptive of exposure-response. To clarify the authors' approach, Dr. Berman indicated that the meta-analysis considered any published epidemiological study with sufficient quantitative exposure data that allowed for a reasonable estimate of the exposure-response relationship; uncertainty factors were than assigned to give greatest weight to the most robust studies. In response, additional panelists concurred with the original comment that meta-analyses conventionally begin with establishing explicit study inclusion criteria. These panelists clarified that they are not advocating removing a majority of studies currently considered in the proposed protocol, but rather being more judicious in selecting the studies to evaluate.

One panelist offered additional comments on the meta-analysis. He supported, for instance, the use of sensitivity analyses, and encouraged the authors to conduct additional analyses to identify influential studies, factors that contribute to risk, and the impact of different weighting factors. The panelist also noted that more sophisticated statistical methodologies (e.g., Bayesian

modeling, Markov Monte Carlo) can be used to generate distributions of outputs, rather than discrete values, which might offer greater understanding of the inferences that can be drawn from the epidemiological studies.

- ***Disparate findings from the South Carolina and Quebec cohorts.*** Multiple panelists noted that the issue of the relative lung cancer potency of chrysotile and amphibole fibers depends largely on how one interprets the disparate findings from the cohort of textile workers in South Carolina and the cohort of chrysotile miners and millers in Quebec. Two of these panelists indicated that the relative potency issue likely will not be resolved until the underlying reasons for the differences between these two studies are better understood. The other panelist viewed the difference in potency observed across industries (i.e., mining versus textile) as a more important matter than the difference between the two specific cohorts. When discussing these studies, two panelists indicated that the increased lung cancer risk for the South Carolina cohort might be attributed to exposure to amphibole fibers, which are known to be found in trace levels in commercial chrysotile.

- ***Relevance of fiber durability.*** One panelist noted that the issue of fiber durability often enters the debate on the relative lung cancer potency of chrysotile and amphibole fibers. Though he agreed that the animal toxicology data indicate that amphibole fibers are more persistent than chrysotile fibers, the panelist noted that trends among the human epidemiological data—particularly the fact that lung cancer risk does not appear to decrease with time since last exposure, even for chrysotile—suggest that the lower durability of the chrysotile fibers might not be important.

- ***Influence of smoking.*** The panelists had differing opinions on how the proposed protocol should address cigarette smoking. In terms of inferences drawn from the epidemiological literature, two panelists noted that very limited data are available on smoking, making quantitative analysis of its interactions with asbestos exposures difficult. Specifically, only one study includes detailed information on smoking, but that study found no difference in lung cancer potency between smokers and non-smokers. During this discussion, Dr. Berman explained that the proposed protocol assumes a multiplicative interaction between smoking and asbestos exposure, consistent with EPA's 1986 model. Dr. Berman noted that a multiplicative factor in the model, α, represents the background risk in the studied cohort relative to the risk in the comparison population, and both groups include smokers; he added that the influence of smoking is addressed implicitly in the model because it is a relative risk model in which the effect of asbestos is multiplied to the background risk that is present. A panelist clarified, however, that neither the potency factors nor α were derived based on observations of smoking prevalence in the epidemiological studies.

  One panelist emphasized that the confounding effects of smoking greatly complicates the analysis of lung cancer potency. He noted that the relative lung cancer risk from asbestos exposure is

considerably lower than that for cigarette smoking. As a result, the panelist wondered how the meta-analysis can truly discern the relative potency of the asbestos fiber types from studies that present no information on cigarette smoking. This panelist provided an example to illustrate his concern: if a given cohort has between 5 and 10% more smokers than the typical population, this increased prevalence of smoking alone could totally confound relative risks attributed to asbestos. The panelist indicated that all future analyses of epidemiological data will suffer from similar limitations, so long as detailed information on smoking is not available.

- ***General comments.*** During this discussion, some panelists offered several general comments that apply to the entire proposed protocol. These comments included concerns about the transparency of the analyses, questions about data tables being inconsistent with text in the body of the report, and some panelists' inability to reproduce certain findings from the available data. These general comments are reflected in the executive summary of this report.

3.1.2 Lung Cancer and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists offered varying insights on the inferences that can, or should, be drawn from animal toxicology studies and mechanistic studies regarding the relative lung cancer potency for chrysotile and amphibole fibers.

Citing various publications (e.g., Lippmann 1994), multiple panelists noted that the animal toxicology studies do not support the 5-fold difference in lung cancer potency between chrysotile and amphibole fibers. Two panelists added that the absence of different potencies might result from the animal studies being of too short duration (typically no longer than 2 years) for the greater dissolution of chrysotile fibers to be an important factor. Another panelist added that exposure levels in some animal studies are not relevant to human exposures; as an example, he noted that a recent rat inhalation study (Hesterberg et al. 1998) involved exposure levels at 11,000 fibers per cubic centimeter. These panelists indicated that the animal studies are generally more informative of how lung cancer potency varies with fiber length (see Section 3.1.4), and are less informative on how potency varies with fiber type.

The panelists noted that *in vitro* studies exhibit various findings, depending on the study design and endpoint assessed. One panelist, for instance, indicated that some *in vitro* studies suggest that chrysotile fibers are actually more potent than amphibole fibers. Other panelists added that many *in vitro* studies show crocidolite being considerably more toxic than chrysotile. These panelist cautioned against drawing firm conclusions from the *in vitro* studies, however, given that the study duration is far too short for any impact of dissolution to be observed. Finally, another panelist referred to the International Agency for Research on Cancer (IARC) consensus statement on fiber carcinogenesis for an overview of inferences that can be drawn from mechanistic studies: "Overall, the available evidence in favor of or against any of these mechanisms leading to the development of lung cancer and mesothelioma in either animals or humans is evaluated as weak" (IARC 1996).

Based on the previous comments, the panelists cautioned about attempting to draw inferences from the animal toxicology for several reasons. One panelist indicated that the animal studies have limited utility because lung cancer in humans results from a complex set of exposures, including cigarette smoke, and because rats, when compared to humans, develop different types of tumors at different sites. Another panelist reiterated that the duration of most animal studies precludes one from observing dissolution effects. Given these limitations, two panelists emphasized that conclusions should be based primarily on the epidemiological data, especially considering the volume of human data that are available. Though not disagreeing with this recommendation, one panelist noted that the exposure index—one of the major outcomes of the proposed protocol—is, in fact, based on observations from animal studies.

3.1.3 Lung Cancer and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists made several observations regarding what can be inferred from the epidemiology literature on how lung cancer potency varies with fiber dimension, though they first noted that most published epidemiology studies do not include detailed data on the distribution of fiber dimensions to which cohorts were exposed. Overall, the panelists generally agreed that indirect evidence from the

epidemiological studies supports the proposed protocol's finding that longer fibers have greater carcinogenic potency for lung cancer. They added, however, that the epidemiology literature provides no evidence to support or refute the magnitude of the relative potencies used in the proposed protocol (i.e., fibers longer than 10 μm being 300 times more potent than those with lengths between 5 and 10 μm). The panelists made no comments about fiber diameter when discussing this matter. Specific discussion topics follow:

- ***Observations from the epidemiology literature.*** The panelists identified several studies that provide general insights on the role of fiber size in lung cancer. One panelist, for instance, noted that cohorts of textile workers, which were believed to be exposed to relatively longer asbestos fibers, exhibit higher lung cancer relative risks than do cohorts of miners or cement product workers. Another panelist indicated that studies of taconite miners from Minnesota (Cooper et al. 1988) and gold miners from South Dakota (McDonald et al. 1978) found no increased lung cancer risks among the cohorts, which were known to be exposed primarily to fibers shorter than 5 μm (see Dr. Case's premeeting comments for further information on these studies). This panelist added that the Minnesota Department of Health is currently updating the study on taconite miners and a publication is pending. Another panelist added that epidemiology studies of workers exposed to asbestos from friction brake products show no clear evidence of increased lung cancer. This panelist acknowledged that these epidemiology studies do not include exposure measurements, but other studies of this work environment have indicated that the asbestos fibers in friction brake products are predominantly short chrysotile fibers.

- ***Relevance of fibrous structures shorter than 5 μm.*** Some panelists noted that no epidemiology studies have examined the relative potency specifically of fibrous structures shorter than 5 μm, thus no conclusions could be drawn from the epidemiology studies alone. While not disagreeing with this observation, one panelist reminded panelists that airborne particles and fibers have a broad distribution of fiber lengths, with a clear majority (75–90%) of fibrous structures being shorter than 5 μm. This panelist added that indirect inferences can be drawn from the epidemiology studies listed in the previous bulleted item. Another panelist noted that the fibrous structures shorter than 5 μm behave more like particles rather than fibers, at least in terms of lung deposition and clearance patterns. Finally, two panelists indicated that an ATSDR expert panel recently evaluated the issue of relative potency of fibers shorter than 5 μm; however, the final report from that expert panel meeting was not available until after the peer consultation workshop. The final report has since been released, and a conclusion from that panel was that "there is a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003).

- ***Statistical analyses in the proposed protocol.*** As indirect evidence that longer fibers have greater carcinogenic potency, one panelist indicated that the exposure-response modeling by Drs. Berman and Crump showed an improved fit to the observed relative risk from epidemiology studies when using an exposure index that assigns greater weight to longer fibers and no risk to fibers shorter than 5 μm. Another panelist concurred, but added that the authors could have attempted to determine the specific weighting (i.e., between longer and shorter fibers) that would optimize the fit to the epidemiological studies.

3.1.4 Lung Cancer and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists generally agreed that the animal toxicology studies and mechanistic studies indicate that fiber dimension—especially fiber length—plays an important role, both in terms of dosimetry and pathogenesis. However, panelists had differing opinions on the specific cut-offs that should be used for fiber diameters and lengths in the exposure-response modeling (though panelists generally concurred that fibers shorter than 5 μm should be assigned zero potency).

- ***Fiber length.*** Multiple panelists noted that the animal toxicology studies provide compelling evidence that lung cancer potency increases with fiber length. Another panelist agreed, but had reservations about assigning no potency to fibrous structures shorter than 5 μm, based on a recent study of refractory ceramic fibers (Bellman et al. 2001) that found that the incidence of inflammation and fibrosis appears to be related to the presence of small fibers in the lung. This panelist indicated that exposure to small fibers likely has some bearing on the oxidative stress state and inflammation in the lung, and he suspected that the exposure-response relationship for long fibers might depend on co-exposures or past exposures to shorter fibers. Based on these observations, the panelist was hesitant to exclude fibrous structures shorter than 5 μm from the proposed risk assessment methodology. On the other hand, another panelist added that animal toxicology studies have shown that fibrosis endpoints are strongly related to fiber length, with exposures to shorter fibers showing less evidence of fibrosis or lung damage. The panelists revisited the significance of fibers shorter than 5 μm when discussing the proposed exposure index (see Section 4).

- ***Fiber diameter.*** The panelists offered several comments on the role of fiber diameter in the proposed protocol. Noting that fibers with diameters up to 1.5 μm are capable of penetrating to sensitive portions of the lung during oral inhalation, one panelist indicated that this range of fiber diameters should not be excluded from future risk assessments. Other panelists shared the

concern of assigning no lung cancer potency to respirable fibers with diameters greater than 0.5 μm, especially considering that respirability patterns in laboratory animals differ from those in humans (i.e., thicker fibers are more likely to deposit in the human lung than they are in the rat lung).

The panelists also discussed a statement in the proposed protocol that "few fibers thicker than 0.7 μm appear to reach the deep lung." First, one panelist indicated that the proposed protocol includes outdated information on fiber deposition patterns; he recommended that the authors obtain more current insights from specific publications (e.g., Lippmann 1994) and from the latest lung dosimetry model developed by the International Commission on Radiological Protection. Second, another panelist questioned the relevance of deposition in the deep lung, because humans tend to develop bronchogenic carcinomas, while rats develop bronchoalveolar carcinomas. Another panelist cautioned against inferring that asbestos fibers must deposit on bronchial airways to cause lung cancer in humans, noting that significant accumulation of asbestos fibers does not occur in the airways where carcinomas develop in humans, due primarily to mucociliary clearance; this panelist suspected that deposition of fibers in the deep lung is likely related to lung cancer formation in humans, though the mechanisms of carcinogenesis are not fully understood.

3.1.5 Other Issues Related to Lung Cancer

The panelists discussed several additional issues related to the proposed protocol's evaluation of lung cancer potency. Most of the discussion focused on the utility of non-linear exposure-response modeling, but other topics were also addressed:

- ***Consideration of non-linear exposure-response models.*** The panelists had differing opinions on the extent to which the proposed protocol should consider non-linear exposure-response modeling. On the one hand, one panelist strongly recommended that EPA consider exploring the applicability of non-linear exposure-response models, given his concerns with linear low-exposure extrapolation. This panelist acknowledged that the revised linear model in the proposed protocol clearly provides an improved statistical fit to the epidemiological data when compared to EPA's 1986 lung cancer model, but he advocated more detailed exploration of non-linear cancer risk models, particularly to account for observations of cohorts with low exposures. This panelist was particularly concerned about the cancer risks that would be predicted for low exposures: because the slope in any linear lung cancer model will be determined largely by highly-exposed individuals, he questioned whether the slope derived from

high exposures truly applies to lowly-exposed individuals. To demonstrate his concern, this panelist indicated that the epidemiological studies consistently show that cohorts (or subsets of cohorts) with low exposure generally exhibit no increased lung cancer risk (standardized mortality ratios not statistically different from 1.0). To account for the possibility of a threshold or non-linearity in the exposure-response relationship, this panelist recommended that EPA investigate alternate exposure-response models, such as linear-linear models (i.e., models with two linear exposure-response regions having different slopes) or log-linear models.

Other panelists generally supported these comments. One panelist, for instance, noted that EPA's Draft Revised Guidelines for Carcinogen Risk Assessment indicates that exposure-response relationships should first be evaluated over the range of exposure observations, and then various approaches to extrapolate to exposure levels outside (i.e., below) this range should be investigated. Another panelist added that some studies finding no evidence of lung cancer risks among large cohorts with low exposures should factor into the decision of whether the lung cancer model should include thresholds; he cited a study of non-occupationally exposed women from chrysotile mining regions in Canada (Camus et al. 1998) to illustrate his concern. Other panelists noted that the utility of this study is limited, because exposures were not measured for individuals; further, a panelist clarified that approximately 5% of the individuals considered in this study were occupationally exposed. Finally, one panelist indicated that evidence from the epidemiology literature strongly suggests there are asbestos exposure levels below which lung cancer will not occur; this panelist added that he is unaware of any epidemiological study that has found evidence of lung cancer risk at exposure levels below 25 fiber-years. He recommended that the proposed protocol at least acknowledge the lowest exposure level at which lung cancer effects have been demonstrated.

On the other hand, some panelists were not convinced of the utility of conducting detailed analyses at low exposures and investigating possible thresholds. One panelist, for instance, indicated that a meaningful quantitative analysis of potential thresholds will not be possible, so long as the authors do not have access to raw data from additional epidemiological studies. Further, this panelist suspected that the protocol authors would find considerable heterogeneity among exposure-response slopes for low exposures, and he questioned what conclusions could be drawn by focusing exclusively on the low exposure region. Another panelist agreed, adding that the failure to find significantly increased cancer risks among lowly-exposed cohorts very likely results from poor statistical power and other uncertainties, and not necessarily from the presence of an actual exposure threshold for asbestos-related lung cancer. Finally, one panelist indicated that the National Institute for Occupational Safety and Health (NIOSH) previously examined a threshold model for the cohort of South Carolina textile workers, and that analysis revealed that the best fit of the exposure-response data was a threshold of zero (i.e., the best fit indicated that there was no threshold).

- ***Consideration of cigarette smoking.*** Several times during the workshop, the panelists debated the ability of the proposed risk assessment model to address interactions between cigarette smoking and asbestos exposure. One panelist recommended that the authors review a recent study that examined the role of cigarette smoking on lung cancer among chrysotile miners and millers in Quebec, Canada (Liddell and Armstrong 2002). Although the panelists generally agreed that smoking is an important consideration for developing and applying the model, some panelists were not convinced that the available data are sufficient to develop an exposure-response model that accurately portrays the interactive effects of asbestos exposure and smoking. The panelists further discussed this issue further later in the workshop.

- ***Transparency of the proposed protocol.*** Several panelists indicated that the review of epidemiological data in the proposed protocol is not presented in a transparent fashion. One panelist, for instance, sought more information on the uncertainty factors used in the meta-analysis, such as what ranges of factors were considered, what criteria were used to assign the factors, and a table of the factors that were eventually applied. This panelist also recommended that the proposed protocol identify the α-values that were determined for each epidemiological study and provide explanations for any cases when these values are unexpectedly large. Another panelist indicated that the proposed protocol should more clearly differentiate conclusions that are based on a meta-analysis of many epidemiological studies from conclusions that are based on a detailed review of just one or two studies.

- ***The need to obtain additional raw data sets.*** The panelists unanimously agreed that EPA should make every effort to try to obtain additional raw data sets for the epidemiology studies, such that the authors can further test how adequately the proposed risk assessment model predicts risk. The executive summary of this report presents the panelists' specific recommendation on this issue.

3.2 Mesothelioma

The following paragraphs document the panelists' responses to charge questions regarding inferences from the epidemiology and toxicology literature on how mesothelioma potency varies with fiber type (Sections 3.2.1 and 3.2.2) and fiber length (3.2.3 and 3.2.4).

3.2.1 Mesothelioma and Fiber Type: Inferences from the Epidemiology Literature

The expert panelists unanimously agreed that the epidemiology literature provides compelling evidence that amphibole fibers have far greater mesothelioma potency than do chrysotile fibers—a finding reported both in the review document (Berman and Crump 2001) and a recent re-analysis of 17 cohort studies (Hodgson and Darnton 2000) that reported at least a 500-fold difference in potency. Two panelists commented further that the epidemiology literature provides no scientific support for chrysotile exposures having a role in causation of mesothelioma—an observation that is generally consistent with the meta-analysis in the proposed protocol, which failed to reject the hypothesis that chrysotile fibers have zero potency for mesothelioma.

The most notable response to this charge question was the agreement among most panelists that amphibole fibers are at least 500 times more potent than chrysotile fibers for mesothelioma, as supported by two separate reviews of epidemiological studies. The panelists made additional comments on specific matters when responding to this question, as summarized below, but the key point in this discussion was the agreement that chrysotile is a far less important cause of mesothelioma than are amphiboles.

- ***Relative roles of chrysotile and amphibole.*** One panelist indicated that cohort studies with individual-level exposure-response data and the broader epidemiology literature both provide no evidence of increased mesothelioma risk due to chrysotile exposure. Further, this panelist noted that 33 of 41 mesothelioma cases previously identified as occurring among workers primarily exposed to chrysotile fibers (Stayner et al. 1996) were later reported as likely resulting from exposures to tremolite fibers found in the chrysotile mines (McDonald et al. 1997). This panelist noted that a recent finding of a small mesothelioma risk from chrysotile (Hodgson and Darnton 2000) results entirely on the assumption that the 33 mesothelioma cases mentioned above result entirely from chrysotile exposures. Based on these observations, this panelist indicated that the literature suggests that chrysotile exposures have limited, if any, role in causing mesothelioma. He nonetheless supported the relative potency attributed to chrysotile in the proposed protocol as a conservative measure in the overall risk assessment process.

- ***Specific comments on the Connecticut friction products workers.*** Another panelist commented on an epidemiological study of a cohort of workers employed at a friction products plant in Connecticut. The panelist noted that the original study (McDonald et al. 1984) did not identify any deaths from mesothelioma, but review of the state cancer registry (Teta et al. 1983)

revealed that three Connecticut residents who died of mesothelioma were employed by the same friction products company. One of these employees had amphibole exposures during the time he worked for a textile plant that was under the same parent company that owned and operated the friction products plant. The other two cases, the panelist noted, were females who indeed worked at the friction products plant. A pathology review found that one of these cases was a woman with probable pleural mesothelioma and 5 years of exposure; the other case was a peritoneal mesothelioma in a woman who also had asbestosis, and worked as a clerk for 30 years. This panelist noted that it was questionable to attribute the latter two mesothelioma diagnoses to the chrysotile exposures at the friction products plant, though she added that this possibility cannot be definitively ruled out. This panelist encouraged that future review of this epidemiological study should be revised given this new information.

- ***Comments on the proposed 500-fold difference in relative potency.*** The panelists had several comments on the finding in the proposed risk assessment methodology that amphibole fibers are 500 times more potent for mesothelioma than are chrysotile fibers. Several panelists noted that this finding is consistent with that of a recent re-analyses of 17 epidemiological studies (Hodgson and Darnton 2000). Though not disagreeing that amphibole fibers are clearly more potent, one panelist was concerned that the risk coefficients (K_M) were largely derived from data sets with inadequate exposure-response information for mesothelioma, and assumptions had to be made to determine critical inputs to the mesothelioma model (e.g., average exposure, duration of exposure).

  Other panelists commented on specific sections in the proposed protocol. One panelist, for example, recommended that the authors check the accuracy of data presented in Table 6-16 and Table 6-29 of the report, which are not reported consistently. Another panelist suggested that the authors better explain why separate risk coefficients for amphiboles and chrysotile were calculated for some cohorts (e.g., Hughes et al. 1987) but not for others (e.g., Berry and Newhouse 1983), even though the exposure information available for the studies appears to be comparable. Finally, one panelist recommended that the authors of the proposed protocol consider questions recently raised (Rogers and Major 2002) about the quality of the exposure data originally reported for the Wittenoom cohort (De Klerk et al. 1989) when evaluating exposure-response relationships for mesothelioma.

3.2.2 Mesothelioma and Fiber Type: Inferences from Animal Toxicology and Mechanistic Studies

The panelists discussed the inferences provided by animal toxicology data and mechanistic data regarding relative mesothelioma potency of different asbestos fiber types. Overall, two panelists

commented that the human epidemiological data clearly establish that exposures to amphibole asbestos fibers pose a greater mesothelioma risk than do exposures to chrysotile fibers. They added that the animal toxicology data are generally supportive of this finding, but the animal data suffer from some limitations. Two panelists, for instance, noted that the utility of animal toxicology studies is limited by the fact that rodents are rather insensitive to mesothelioma. These panelists added that the animal toxicology studies involving intra-tracheal instillation or peritoneal injection are not directly relevant to the inhalation exposures that occur in humans. These limitations notwithstanding, the panelists raised the following points when discussing the animal toxicology and mechanistic studies:

One panelist referred to one of his earlier publications (Lippmann 1994) for further insights on the occurrence of mesothelioma in animal studies. At that time, this panelist noted, the animal inhalation studies found fewer than 10 cases of mesothelioma, and the number of cases appeared to be greatest among animals that were exposed to mixtures containing higher proportions of amphibole fibers. He found this consistent with the influence of fiber type observed in the human epidemiological data (see Section 3.2.1).

During this discussion, one panelist reviewed a publication (Suzuki and Yuen 2001) that was mentioned earlier in the workshop. The publication documents the amounts and types of asbestos fibers measured in samples of pleural plaques and tumor tissue collected for legal cases. These analyses reportedly found relatively large amounts of short, thin chrysotile fibers in the pleura, suggesting that these fibers should not be excluded from the group of fibers believed to induce mesothelioma. The panelist had several criticisms of the study. First, he indicated that the samples were analyzed using a non-standard technique, without any controls. Second, he questioned the major finding of fibers being detected in the pleura, because most of the samples analyzed were actually tumor tissue, in which he would not expect to find fibers. The panelist suspected that the chrysotile fibers reportedly found in the study likely result from specimen contamination—a bias that would have been more apparent had rigorous quality control procedures been followed. Finally, the panelist noted that a more rigorous study (Boutin et al. 1996) of

asbestos fibers in the parietal pleura found a mixture of fibers, including long amphibole fibers, among living patients with asbestos-related conditions. Based on these concerns, the panelist concluded that the publication of concern (Suzuki and Yuen 2001) is seriously flawed and its recommended should be excluded from EPA's analyses.

A specific issue raised regarding the analytical technique in the study (Suzuki and Yuen 2001) was that water was used during the digestion process. Noting that water may contain large amounts (>30,000 fibers/L) of small asbestos fibers, another panelist suspected that the fibers detected in the study might have resulted from contamination introduced during the digestion process. Because control samples were not analyzed, the panelist said the study offers no evidence that the fibers detected truly were in the original pleural plaques or tumor tissues. He added that studies of lung-retained asbestos fibers routinely detect primarily short, chrysotile fibers, and that the presence of the short fibers in the pleural tissue—even if the measurements from the study are valid—would not necessarily prove that short fibers cause mesothelioma.

3.2.3 Mesothelioma and Fiber Dimension: Inferences from the Epidemiology Literature

The panelists commented briefly on how the human epidemiological data characterize the role of fiber size on mesothelioma risk. Noting that exposure measurements in most every epidemiological study do not characterize fiber length distribution, one panelist indicated that these studies provide no direct evidence of how fiber length is related to mesothelioma. He added that the studies offer conflicting indirect evidence of the role of fiber length. Specifically, the higher mesothelioma risk coefficient among textile workers in South Carolina, when compared to that for the chrysotile miners and millers in Quebec, could be supportive of longer fibers being more potent, since exposures in South Carolina had a larger percentage of long fibers. However, a cohort of cement plant workers in New Orleans was found to have a higher mesothelioma risk coefficient than that of the South Carolina cohort, even though the South Carolina workers were exposed to higher percentages of long fibers. Finally, as indirect

evidence that carcinogenic potency increases with fiber length, this panelist noted that the mesothelioma risk model using the proposed exposure index, which is heavily weighted by long fibers, provided a considerably improved fit to the epidemiological data.

The panelists briefly revisited the inferences that can be drawn from studies of lung-retained fibers. One panelist again commented that results from a recent study (Suzuki and Yuen 2001) should be viewed with caution. He added that several other lung pathology studies (e.g., McDonald et al. 1989, Rogers et al. 1991, Rödelsperger et al. 1999) have been conducted using more rigorous methods, such as using appropriate controls for age, sex, and hospital. These studies all showed that risk of mesothelioma was considerably higher for individuals with larger amounts of long fibers retained in their lungs.

One panelist indicated that results from a study of lung-retained fibers (Timbrell et al. 1988) suggest fiber diameter plays a rule in mesothelioma risk: the study observed no mesothelioma cases among a population highly exposed to anthophyllite fibers, which tend to be thicker fibers. Citing his earlier review of mesothelioma cases (Lippmann 1988), the panelist also noted that crocidolite fibers are both thinner than and more potent than amosite fibers, which further supports the hypothesis that carcinogenic potency for asbestos decreases with increasing fiber diameter.

3.2.4 Mesothelioma and Fiber Dimension: Inferences from Animal Toxicology and Mechanistic Studies

The panelists made few observations on findings from animal toxicology studies regarding mesothelioma and fiber length. One panelist indicated that findings from the animal toxicology studies generally support the overall finding that mesothelioma risks are greatest for long, thin fibers. However, another panelist noted that his earlier review of mesothelioma risks (Lippmann 1988) hypothesized that the critical fibers for mesothelioma induction are those with lengths between 5 and 10 μm. This panelist added that fibers of this dimension are more likely to translocate to the pleura than are longer fibers, but

he acknowledged that it is unclear whether fibers must first translocate to the pleura in order to cause mesothelioma.

Some panelists indicated that fiber durability likely plays a role in inducing mesothelioma, based on the fact that mesothelioma is more easily induced in animals using administration methods (e.g., peritoneal injection) that remove the importance of dissolution.

3.3 Exposure Estimates in the Epidemiology Literature

The panelists raised numerous issues when responding to the third charge question: "To what extent are the exposure estimates documented in the asbestos epidemiology literature reliable?" Recognizing that the exposure estimates from the epidemiology studies are critical inputs to the exposure-response assessment, the panelists expressed concern about the exposure data: few studies provide detailed information on fiber size distribution; many studies report exposures using outdated sampling and analytical methodologies (e.g., midget impinger); individual-level data are not available for most studies; and many studies do not report detailed information on parameters (e.g., exposure levels, exposure duration) needed to evaluate exposure-response relationships, particularly for mesothelioma. Their specific concerns on these and other matters follow:

- ***Concerns regarding exposure estimates in specific studies.*** Some panelists expressed concern about the assumptions made to interpret the exposure data originally reported in the epidemiology studies. One panelist reviewed specific examples of these concerns:
  - The original study of workers at a Connecticut friction products plant (McDonald et al. 1984) reports exposures measured by midget impingers (in units of mmpcf), with no information on how to convert this to PCM measurements, and the original publication includes limited data on exposure duration.
  - The original study of workers at a New Jersey insulation factory (Seidman et al. 1986) did not report any exposure measurements from the factory studied, and data collected

from another plant with similar operations were used to characterize exposure-response for this cohort.

- The original study of workers at a Texas insulation factory (Levin et al. 1998) reported a range of exposure levels (15–91 fibers/mL), and the authors of the proposed protocol assigned an average exposure level (45 fibers/mL) to the entire cohort.

- The original study of U.S. insulation applicators (Selikoff and Seidman 1991) has no information on exposure. The proposed protocol assumes that all workers were exposed to 15 fibers/mL for 25 years, based on a separate review of exposures among insulation workers (Nicholson 1976).

- The original study of retirees from the U.S. Asbestos Products Company (Enterline et al. 1986) reported exposures based on midget impinger sampling, with no information on how to convert these exposures to PCM measurements.

- According to a recent letter to the editor (Rogers and Major 2002), the original study of the Wittenoom cohort (De Klerk et al. 1989) might have overestimated exposures, possibly by as much as a factor of 10.

The previous comments led to a discussion on whether certain studies should be excluded from the meta-analysis used in the proposed protocol (see next bulleted item). Prior to this discussion, one panelist expressed concern about being overly critical of the exposure estimates used for many of the studies listed above; he emphasized that all exposure estimates appear to be based on a critical review of the literature, and no estimates are completely arbitrary, as some of the panelists' comments implied.

- ***Comments on using study inclusion criteria for the meta analysis.*** Given the concerns about the quality of exposure data reported in some epidemiology studies, the panelists debated whether future revisions of the proposed protocol should exclude certain studies from the exposure-response analysis. The panelists were divided on this matter.

  On the one hand, several panelists recommended that the authors develop and apply study inclusion criteria in the exposure-response evaluation, as is commonly done when conducting a meta-analysis. One panelist, for instance, recommended assessing exposure-response relationships for only those studies found to have adequate exposure data, and then using a sensitivity analysis to examine the effect of excluding studies with inadequate exposure data. These panelists clarified that they are not advocating disregarding the majority of studies; rather, they are suggesting simply that the authors of the proposed protocol use study inclusion criteria and sensitivity analyses to ensure that the conclusions are based on the best available exposure data.

On the other hand, several panelists supported the current approach of using as many studies as possible and accounting for the quality of the exposure measurements in the uncertainty factors. One panelist, for example, commended the authors for being as inclusive as possible when reviewing the studies; he supported the approach of recognizing the limitations of the available exposure data and accounting for these limitations in the uncertainty factors that were ultimately used to weight the studies in the meta-analysis. This panelist acknowledged that the exposure estimates in some of the epidemiological studies might be rough estimates, but he emphasized that the estimates are not worthless and should not be discarded. Other panelists concurred with these comments, and did not support applying overly restrictive study inclusion criteria.

- ***Comments on the uncertainty factors assigned to each study.*** The panelists made several comments on the uncertainty factors that the authors assigned to each study. Dr. Berman first explained the four uncertainty factors: the first factor (F1) characterizes the confidence in exposure estimates; the second factor (F2) represents the confidence in the conversion to PCM measurements from other exposure metrics (typically midget impinger analyses); the third factor (F3) characterizes the confidence the authors had on worker history data; and the fourth factor (F4) was a non-exposure related factor to account for other uncertainties (e.g., lack of information on confounders, incomplete or inaccurate mortality ascertainment). Dr. Berman described generally how the individual uncertainty factors were assigned and noted that each factor could range from 1 to 5.

  The panelists' comments primarily focused on the transparency of how uncertainty factors were presented and incorporated into the meta-analysis. Multiple panelists, for instance, recommended that future revisions to the proposed protocol include a table that lists the uncertainty factors assigned to each study. Further, one panelist suggested that the revised protocol describe the assumptions inherent in the uncertainty factor weighting approach, such as explaining why some factors are assigned values over a broader range than others (e.g., why F1 values span a broader range than F4 values) and describing why the individual uncertainty factors have equal weights in generating the composite uncertainty factor. Another panelist agreed, and added that the revised protocol should more explicitly describe how the uncertainty factors were combined into the composite factor and how this composite factors affects the weighting of studies in the meta-analysis. Expanding on this point, another panelist suggested that the final document more clearly explain that the final estimates of cancer risk coefficients (K_L* and K_M*) are actually weighted averages of the epidemiological studies, with the weights assigned to each study being a function of that study's uncertainty. This panelist also recommended that the revised document clearly state how, if at all, the fraction of amphibole fibers and the fraction of fibers longer than 10 μm are reflected in the uncertainty factors.

  Some panelists debated the utility of alternate approaches that could be used to assign uncertainty factors. Two panelists noted that the approach used to assigning uncertainty factors is somewhat subjective, because different groups of analysts would likely assign different

uncertainty factors. To avoid the appearance of arbitrariness, these panelists suggested using alternate meta-analysis approaches that do not require using uncertainty factors. They noted, for example, that the authors could use a random effects model in which residual inter-study variation is estimated. Another suggestion was to conduct sensitivity analyses examining the effects of including or excluding studies, depending on the uncertainty factors assigned to them.

Another panelist disagreed with these comments and supported the analyses in the proposed protocol; this panelist indicated that the authors had no choice but to make judgments based on the information documented in the epidemiology literature. He suggested that EPA consider convening a separate expert panel to assign uncertainty factors, if panelists do not support those selected by Drs. Berman and Crump.

- ***Assumptions made to convert exposure estimates from midget impinger sampling.*** Several panelists noted that the original publications for many epidemiology studies document exposure estimates based only on midget impinger sampling and do not include any information on how to convert these exposures to levels that would be measured by more modern methods (e.g., PCM, TEM). The panelists noted that the conversion factor (from mmpcf to fibers/mL) can vary considerably from one occupational setting to the next.

- ***Interpretations of the study of South Carolina textile workers.*** The panelists had different opinions on interpretations of the study of South Carolina textile workers (Dement et al. 1994). One panelist, for instance, found this particular study to be an outlier among the other epidemiological studies, and he recommended that the authors exclude this study from the exposure-response analysis until the causes for the increased relative risks observed for this cohort are better understood. Another panelist suggested that the proposed protocol should classify the South Carolina cohort as being exposed to mixed asbestos fibers, rather than being exposed to chrysotile fibers. He indicated that some workers in the cohort were exposed to amosite and crocidolite, in addition to being exposed to chrysotile.[1]

  Other panelists, however, did not think the South Carolina study should be excluded from EPA's analysis. One panelist was troubled about criticisms of the exposure estimates for this cohort, given that this is one of few studies in which co-located samples were collected and analyzed using different methods, thus providing site-specific data for converting midget impinger

[1] After reviewing a draft of this report, one panelist indicated that it is important to note that exposure data for the South Carolina cohort are available from more than just one reference (Dement et al. 1994). He suggested that EPA use data from studies conducted by McDonald in the 1980s of a parallel cohort in the same plant. However, he cautioned EPA against treating multiple studies of the same relatively small group of workers as separate studies, considering the large overlap of workers studied by the two groups of investigators. This panelist encouraged EPA to consider other data sources for this cohort, given that a recent re-analysis of epidemiological studies (Hodgson and Darnton 2000) severely criticized the data source EPA uses (Dement et al. 1994), to the point of those data being dropped from the recent re-analysis altogether.

sampling results to PCM measurements. Another panelist challenged suggestions that the South Carolina study is an outlier; he indicated that the South Carolina study is one of the more rigorous epidemiology studies available for asbestos exposures, and he found no valid scientific reasons for discarding it. During this discussion, one panelist point out in response that the South Carolina study is indeed an outlier among the textile cohorts, with a slope which is higher than either of the two textile cohorts; this panelist did acknowledge that the lung cancer risk among the textile cohorts is greater than that among the mining cohorts. This panelist added that scientists need a better explanation for why the lung cancer risk among the South Carolina cohort is greater than that of other cohorts before the South Carolina study can achieve credibility, especially considering that exposures in South Carolina were supposedly to "pure" chrysotile.

4. COMMENTS ON TOPIC AREA 2: THE PROPOSED EXPOSURE INDEX

This section summarizes the panelists' responses to the charge questions pertaining to the proposed exposure index. Section 4.1, 4.2, and 4.3 document the panelists' responses to charge questions 4, 5, and 6, respectively.

4.1 Responses to Charge Question 4

Charge question 4 asks: "The proposed exposure index does not include contributions from fibers shorter than 5 μm. Please comment on whether the epidemiology and toxicology literature support the conclusion that asbestos fibers shorter than 5 μm present little or no carcinogenic risk." The panelists discussed this matter earlier in the workshop (see Sections 3.1.3 and 3.1.4 for these comments), and provided additional insights on the matter. Overall, the panelists agreed that carcinogenic potency increases with fiber length, particularly for lung cancer. Most panelists supported assigning no potency to fibrous structures smaller than 5 μm. Some panelists agreed that the short fibrous structures are clearly less potent than long fibers, but they had reservations about assigning zero potency to the structures smaller than 5 μm; these panelists acknowledged that the toxicity of the short fibrous structures might be adequately addressed by EPA's air quality standards for particulate matter. Specific comments on this charge question follow:

- ***Reference to ATSDR's expert panel workshop on the role of fiber length.*** Two panelists noted that ATSDR convened an expert panel in October 2002 to discuss the role of fiber length on toxicity, and much of that discussion specifically addressed fibrous structures smaller than 5 μm. A main conclusion of that panel was that there is "a strong weight of evidence that asbestos and synthetic vitreous fibers shorter than 5 μm are unlikely to cause cancer in humans" (ERG 2003). The panelists encouraged EPA to review the summary report prepared for that workshop, which was officially released on March 17, 2003, and is available on-line at: www.atsdr.cdc.gov/HAC/asbestospanel.

- ***Evidence from epidemiological studies.*** One panelist indicated that the epidemiological studies do not provide direct evidence of the role of fibrous structures shorter than 5 μm.